Pregnancy, Childrearing, and Risk of Stroke in Chinese Women

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Background and Purpose—Although it has been suggested that high gravidity and parity increase the risk for coronary heart disease, their associations with stroke are unclear.

Methods—We evaluated associations of gravidity and parity with incidence of stroke in the Shanghai Women's Health Study (SWHS), a population-based cohort study of 74,942 Chinese women aged 40 to 70 years at enrollment (1996 to 2000). We also examined the association between number of children and stroke prevalence in both SWHS participants and their husbands. Stroke cases were ascertained through in-person interviews and linkage with vital statistics registries.

Results—During a mean follow-up of 7.3 years, 2,343 incident cases of stroke were identified. Women with more pregnancies or live births had a significantly increased risk for incident stroke. After adjustment for socioeconomic status and other potential confounders, women with ≥5 pregnancies had a hazard ratio for incident stroke of 1.45 (95% CI, 1.18 to 1.77) compared with those with only one pregnancy. At baseline recruitment, 859 and 1274 prevalent cases of stroke were reported among SWHS participants and their husbands, respectively. Stroke prevalence increased with increasing number of children in both women and men. Adjusted ORs of prevalent stroke for having ≥5 children versus having one child were 1.61 (95% CI, 1.16 to 2.23) in women and 1.45 (1.11 to 1.89) in men.

Conclusions—High gravidity or parity may be related to increased risk of stroke in women. Chronic stress and adverse lifestyle factors related to childrearing may contribute importantly to the increased risk. (Stroke. 2009;40:2680-2684.)

Key Words: pregnancy ▪ stroke ▪ women

High gravidity and high parity have been linked to an increase in adiposity, insulin resistance, dysglycemia, dyslipidemia, and metabolic syndrome in women.1–4 Whether the adverse metabolic changes associated with pregnancy predispose women to cardiovascular disease in later life remains controversial.1,2,5–8 Several epidemiological studies have evaluated associations of gravidity and parity with risk of cardiovascular disease, particularly coronary heart disease, in middle-aged and elderly women. The results from these studies have been inconsistent with some reporting significant positive associations2,5,6 and others showing no association.7,8 Very few studies have specifically investigated stroke risk in relation to reproductive history in women.

Childrearing is known to be associated with elevated levels of stress and anxiety and unfavorable changes in lifestyles, which may increase the risk for cardiovascular disease.1,2,6 This raises the question of whether factors related to childrearing, rather than pregnancy per se, may underlie the association between gravidity or parity and cardiovascular disease in women. Few studies have addressed this important issue.

We examined numbers of pregnancies and live births in relation to incidence of stroke in a large cohort of Chinese women enrolled in the Shanghai Women’s Health Study (SWHS). We also evaluated the association between number of children and stroke prevalence in both SWHS participants and their husbands to address the issue of childrearing as a potential mediator of the gravidity/parity and stroke association in women.

Study Population

The SWHS is a population-based, prospective cohort study of adult Chinese women. The study methods have been described in detail elsewhere.9 Briefly, all eligible women 40 to 70 years of age and living in 7 typical urban communities of Shanghai were invited to participate in the study. Between December 1996 and May 2000, a total of 74,942 women enrolled in the study and completed the baseline survey (participation rate, 92.7%). The baseline survey was conducted at participants’ homes by trained interviewers. Structured questionnaires were used during the survey to obtain information on demographics, lifestyle habits, menstrual and reproductive history, use of oral contraceptives and hormone therapy, medical history, and other characteristics. Anthropometric measurements were also taken.

Over 99% of SWHS participants were married. As part of the baseline survey, all married women were also asked to provide...
information on their husbands’ demographic background, lifestyle, and medical history. Husbands were invited to participate in the interviews whenever possible. The study was approved by the Institutional Review Boards of all institutes involved, and written, informed consent was obtained from all participants.

Assessment of Reproductive History
During the baseline in-person interviews, each participant was asked whether she had ever been pregnant and, if so, how many times followed by questions on specific details of each pregnancy, including the date the pregnancy ended, the length of the pregnancy, and the pregnancy’s outcome (eg, live birth, stillbirth, miscarriage, or induced abortion).

Outcome Ascertainment
Participants were followed every 2 years through home visits and record linkage to the Shanghai Cancer Registry and the Shanghai Vital Statistics Registry. During the biennial home visits, trained study interviewers conducted in-person interviews using a structured questionnaire that captured information on newly diagnosed major chronic diseases. For subjects who had died, an adult family member (next of kin) was interviewed to complete the disease outcome survey. The primary outcome for the present analysis was incident stroke, defined as the first nonfatal stroke or stroke death that occurred after the baseline survey. The occurrence of stroke was ascertained by asking the following question: “Since our last visit, have you suffered a stroke that was confirmed by a doctor?” For each positive response, information on the date and hospital of the first diagnosis was obtained. Information on major stroke subtypes, including ischemic stroke and intracerebral hemorrhage, was also collected through in-person interviews starting with the second follow-up. In addition to the biennial home visits, disease outcomes and deaths were also ascertained through record linkages. The underlying cause of death was determined on the basis of death certificates and information gathered from next of kin.

To evaluate the validity of stroke ascertained through interviews, medical records were obtained and reviewed by independent physicians for 225 participants who reported a first-ever stroke during follow-up interviews. Brain imaging, including CT or MRI, was available for 95% of these reported stroke cases. The diagnosis of stroke was confirmed according to the criteria of the US National Survey of Stroke, which requires evidence of sudden or rapid onset of neurological deficits that persist for >24 hours or until death and have no apparent nonvascular causes such as trauma, tumor, or infection. Based on review of clinical information and imaging data, 203 (90.2%) stroke cases were confirmed, including 177 cases of ischemic stroke, 22 intracerebral hemorrhage, and 4 subarachnoid hemorrhage. Nine (4.0%) reported stroke cases did not meet the defined criteria for confirmation. Medical documentation was lacking or insufficient to confirm the diagnosis for the remaining 13 (5.8%) cases.

Statistical Analysis
Of the 74,942 SWHS participants, only 2507 (3.4%) had never had a live birth, and they were excluded from the present study to avoid potential bias from health-related factors that might have led to childlessness. To examine the association between reproductive history and incidence of stroke, we further excluded women who had no apparent nonvascular causes such as trauma, tumor, or infection. Based on review of clinical information and imaging data, 203 (90.2%) stroke cases were confirmed, including 177 cases of ischemic stroke, 22 intracerebral hemorrhage, and 4 subarachnoid hemorrhage. Nine (4.0%) reported stroke cases did not meet the defined criteria for confirmation. Medical documentation was lacking or insufficient to confirm the diagnosis for the remaining 13 (5.8%) cases.

The mean age (SD) of the study participants at enrollment was 51.8 years (8.8). The mean number (SD) of pregnancies per woman was 2.8 (1.4) with a range of 1 to 12; and the mean number (SD) of live births per woman was 1.7 (1.1) with a range of 1 to 10. Table 1 presents age-adjusted characteristics of the study population according to the number of pregnancies. Very few women in this population ever smoked cigarettes, drank alcohol, or used hormone therapy, possibly because of Chinese cultural norms. Compared with women with only 1 pregnancy, women with multiple pregnancies were, in general, older and more likely to have low levels of education, family income, or occupational status. They were also more likely to have ever smoked cigarettes or consumed alcohol. In addition, they tended to have a higher body mass index (BMI) and higher prevalence of hypertension or diabetes. The percentage of women who used oral contraceptives was higher in women with more pregnancies, which was likely due to the fact that the use of intrauterine device for contraception was less common in women with more pregnancies than those with fewer pregnancies.

During a mean follow-up of 7.3 years, we identified 2343 incident cases of stroke, including 2206 nonfatal strokes and 137 deaths from stroke. These cases were further classified as ischemic stroke (n=1698), intracerebral hemorrhage (n=200), and undefined stroke (n=445). Table 2 summarizes the HRs and 95% CIs of incident stroke according to the numbers of pregnancies and live births. In both age- and multivariable-adjusted analyses, greater numbers of pregnancies or live births were associated with significantly increased risk of incident stroke in a dose–response fashion. Women with ≥5 pregnancies had a multivariable-adjusted HR for incident stroke of 1.45 (95% CI, 1.18 to 1.77) compared with those with only one pregnancy. The multivariable-adjusted HR was 1.38 (95% CI, 1.12 to 1.69) for women who had ≥5 live births compared with those having one live birth. These risk estimates were attenuated but remained statistically significant after additional adjustment for potential mediators, including body mass index and history of hypertension and diabetes. Additional adjustment for dyslipidemia did not appreciably alter the results. Further stratified analyses revealed that the association between number of pregnancies and stroke risk did not vary materially by age, birth calendar.
In addition, analyses of major stroke subtypes found positive associations similar to total stroke with multivariable-adjusted HRs comparing 5 pregnancies versus one pregnancy of 1.42 (95% CI, 1.11 to 1.80), 1.27 (0.67 to 2.43), and 1.68 (1.03 to 2.74) for ischemic stroke, intracerebral hemorrhage, and undefined stroke, respectively. We also examined age at first pregnancy in relation to stroke risk and found no association after accounting for number of pregnancies.

There were 859 and 1274 prevalent cases of stroke reported at baseline among SWHS participants and their husbands, respectively. Table 3 presents the ORs of prevalent stroke associated with the number of children in women and their husbands. Similar to the findings on incident stroke in women, the ORs for prevalent stroke also increased with increasing number of children in both women and husbands. After adjusting for socioeconomic status and other potential confounders, the ORs of prevalent stroke for having ≥5 children versus having one child were 1.61 (95% CI, 1.16 to 2.23) in women and 1.45 (1.11 to 1.89) in husbands. Additional control for body mass index, hypertension, and diabetes, again, weakened the positive association for women but not for husbands.

**Discussion**

In this large, population-based cohort study, we found that having more pregnancies or live births was associated with a significantly elevated risk of incident stroke in women. In addition, we found a significant positive association between number of children and prevalence of stroke not only in women, but also in their husbands. These positive associations persisted after accounting for sociodemographic factors and other potential confounding variables. Additional adjustment for body mass index, hypertension, and diabetes attenuated the positive association for women, but not for husbands, suggesting that these factors may be potential biological mediators of the parity and stroke association in women. The positive association between number of children and stroke found in husbands, on the other hand, indicates that factors other than pregnancy per se may also have contributed to the observed excess risk of stroke in women with high gravidity or parity. To our knowledge, this is the first study that has simultaneously evaluated the association between number of children and stroke in women and men allowing evaluation of hypotheses beyond the direct biological effects of pregnancy.

The findings of our study are consistent with those of previous studies linking greater number of pregnancies with greater risk of stroke in women beyond typical childbearing age. For example, an analysis of women 45 to 74 years of age in the First National Health and Nutrition Examination Survey Epidemiological Follow-up Study showed that women with ≥6 pregnancies had a 70% increased risk of...
stroke compared with those who had never been pregnant. As seen in our study, adjustment for stroke risk factors reduced, but did not eliminate, the positive association between gravidity and stroke. An earlier British study of middle-aged and elderly women also found a higher mortality rate from cerebrovascular disease in parous women than in nulliparous women. In addition, there are also reports of positive associations of parity with both carotid atherosclerosis and carotid intima media thickness, which are strong predictors of stroke. In contrast to these findings, a few case–control studies of subarachnoid hemorrhage in relatively younger women suggested a potentially protective effect for parity. We have no specific information on subarachnoid hemorrhage. In stratified analyses, we found no modifying effect of age on the association between parity and total stroke.

Although the adverse metabolic changes induced by repeated pregnancies provide biological plausibility for the increased risk of stroke associated with increasing gravidity or parity in women, our observation of a positive association between number of children and stroke prevalence in both women and their husbands suggests that explanations other than the biological consequences of pregnancy may also need to be considered when interpreting study results on childbearing history and stroke risk. Childrearing may increase anxiety levels because of increased responsibilities, sleep deprivation, and financial and occupational stress. Childrearing has also been associated with adverse changes in lifestyle such as unhealthy dietary habits and physical inactivity. These childrearing-related anxiety, stress, and adverse lifestyle factors may contribute importantly to the elevated risk of stroke associated with high gravidity or parity. However, these

Table 2. HRs of Incident Stroke According to Numbers of Pregnancies and Live Births

<table>
<thead>
<tr>
<th>No. of Pregnancies</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>≥5</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>11 033</td>
<td>20 293</td>
<td>16 173</td>
<td>9707</td>
<td>7674</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>130</td>
<td>349</td>
<td>517</td>
<td>595</td>
<td>752</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted HR</td>
<td>1.00</td>
<td>1.16 (0.94–1.41)</td>
<td>1.29 (1.06–1.57)</td>
<td>1.55 (1.27–1.89)</td>
<td>1.70 (1.39–2.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariate HR*</td>
<td>1.00</td>
<td>1.14 (0.93–1.39)</td>
<td>1.21 (0.99–1.47)</td>
<td>1.39 (1.13–1.69)</td>
<td>1.45 (1.18–1.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariate HR†</td>
<td>1.00</td>
<td>1.10 (0.91–1.37)</td>
<td>1.18 (0.97–1.44)</td>
<td>1.35 (1.10–1.65)</td>
<td>1.38 (1.12–1.69)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

No. of Live Births

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>≥5</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>38 816</td>
<td>13 650</td>
<td>6341</td>
<td>3613</td>
<td>2460</td>
</tr>
<tr>
<td>No. of cases</td>
<td>434</td>
<td>618</td>
<td>577</td>
<td>398</td>
<td>316</td>
</tr>
<tr>
<td>Age-adjusted HR</td>
<td>1.00</td>
<td>1.22 (1.13–1.53)</td>
<td>1.67 (1.41–1.98)</td>
<td>1.72 (1.43–2.06)</td>
<td>1.80 (1.48–2.18)</td>
</tr>
<tr>
<td>Multivariate HR*</td>
<td>1.00</td>
<td>1.23 (1.05–1.43)</td>
<td>1.37 (1.15–1.64)</td>
<td>1.34 (1.11–1.63)</td>
<td>1.36 (1.12–1.69)</td>
</tr>
<tr>
<td>Multivariate HR†</td>
<td>1.00</td>
<td>1.20 (1.03–1.40)</td>
<td>1.31 (1.10–1.56)</td>
<td>1.30 (1.07–1.58)</td>
<td>1.27 (1.03–1.55)</td>
</tr>
</tbody>
</table>

*Stratified on birth calendar year and adjusted for age, education, occupation, family income, oral contraceptive use, menopausal status, hormone therapy use, cigarette smoking, and alcohol consumption.
†Additionally adjusted for body mass index and history of hypertension or diabetes.

Table 3. ORs of Prevalent Stroke According to Number of Children in Women and Their Husbands

Women

<table>
<thead>
<tr>
<th>No. of Children</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>≥5</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>40 801</td>
<td>15 898</td>
<td>7871</td>
<td>4645</td>
<td>3220</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>109</td>
<td>221</td>
<td>192</td>
<td>173</td>
<td>164</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted OR</td>
<td>1.00</td>
<td>1.24 (0.95–1.62)</td>
<td>1.27 (0.95–1.70)</td>
<td>1.62 (1.20–2.20)</td>
<td>2.01 (1.47–2.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariate OR*</td>
<td>1.00</td>
<td>1.17 (0.89–1.53)</td>
<td>1.06 (0.79–1.43)</td>
<td>1.31 (0.95–1.79)</td>
<td>1.61 (1.16–2.23)</td>
<td>0.002</td>
</tr>
<tr>
<td>Multivariate OR†</td>
<td>1.00</td>
<td>1.14 (0.87–1.49)</td>
<td>1.03 (0.76–1.39)</td>
<td>1.29 (0.93–1.77)</td>
<td>1.47 (1.06–2.05)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Husbands

| No. of subjects | 38 527 | 14 426 | 6456 | 3559 | 2251 |
| No. of cases | 190 | 321 | 319 | 240 | 204 |
| Age-adjusted OR | 1.00 | 1.09 (0.88–1.34) | 1.47 (1.17–1.84) | 1.64 (1.29–2.09) | 1.93 (1.50–2.50) | <0.0001 |
| Multivariate OR* | 1.00 | 1.04 (0.84–1.28) | 1.22 (0.97–1.54) | 1.27 (0.99–1.63) | 1.45 (1.11–1.89) | 0.002 |
| Multivariate OR† | 1.00 | 1.04 (0.84–1.28) | 1.23 (0.98–1.56) | 1.23 (0.95–1.59) | 1.48 (1.13–1.95) | 0.002 |

*Stratified on birth calendar year and adjusted for age, education, occupation, family income, oral contraceptive use, menopausal status, and hormone therapy use for women.
†Additionally adjusted for body mass index and history of hypertension or diabetes.
Factors are difficult to measure or properly address in studies involving women only. Incorporating data on men, particularly spouses, offers a useful approach to the evaluation of such alternative explanations.

Socioeconomic status is known to be related to both number of children and stroke risk, and its confounding effect is a major concern in evaluating the association between parity and stroke. Although we cannot rule out the possibility of residual confounding by socioeconomic status, we adjusted for education, income, and occupation and found that such adjustments attenuated, but did not eliminate, the significant associations. We did not collect information on pregnancy complications and thus were unable to account for their potential effects on the results. Pregnancy complications such as gestational diabetes and pre-eclampsia/eclampsia have been associated with an elevated risk of stroke in later life. These complications are likely to have reduced the number of subsequent pregnancies. Thus, the association between number of pregnancies or live births and stroke observed in our study may have been underestimated. Another concern is possible misclassification of stroke, because stroke outcome in our study was assessed through in-person interviews without further verification by review of medical records. However, our validation study indicated that stroke assessment through in-person interviews in our cohort was accurate. Previous studies have also shown that even with a self-administered questionnaire, stroke, a life-threatening medical emergency, can be assessed reasonably well.19 Nevertheless, certain self-reported stroke cases could be false-positives, and such random misclassification of outcome might have attenuated the associations. Another limitation of the study is that because of differences in sociodemographic and lifestyle factors, the findings of our study conducted in urban Shanghai may not be generalizable to other populations. Finally, to further address the potential contribution of lifestyle risk factors associated with childrearing to stroke risk, it would be interesting to evaluate the association between number of adopted children and stroke risk in future studies.

In summary, our study indicates that high gravidity and high parity were associated with increased risk of stroke in women. Although the biological effects of pregnancy may account for this positive association, chronic stress and lifestyle risk factors related to childrearing may also be important contributing factors.

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Disclosures
None.

References
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